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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/668,035	09/22/2003	Dominic P. Behan	AREN-005CON (5.US10.CON)	2177

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EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	
MAIL DATE	**DELIVERY MODE**
09/23/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/668,035	BEHAN ET AL.	
	Examiner	Art Unit	
	RUIXIANG LI	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-3,8-10 and 20-25* is/are pending in the application.

5a) Of the above claim(s) *9* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-3,8,10 and 20-25* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignment*.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

Applicant's amendment filed on 05/31/2011 has been entered. In view of the petition decision, the intraclaim restriction requirement set forth on 13 may 2010 requiring applicant to elect a single GPCR of Markush claim 8 has been withdrawn and replaced with an election of species requirement. The elected GPR3 (SEQ Id NO: 46) will continue to be starting place for examination.

Claims 1-3, 8-10, and 20-25 are pending. Claims 1-3, 8, 10, and 20-25 are under consideration. Claim 9 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species.

Withdrawn Objections and/or Rejections

The objection of claims 1-3, 8, 10, 20, 21, and 23-25 for reciting non-elected orphan GPCRs is withdrawn.

The rejection of claims 8 and 22 under 35 U.S.C. 103(a) as being unpatentable over Li et al. (U.S. Patent No. 5,998,164, Dec. 7, 1999; 102 (e) date: June 6, 1995) in view of Seifert et al (J. Biol. Chem. 273: 5109-5116, February 27, 1998) and Eggerick et al. (Biochem. J. 309:837-843, 1995) is withdrawn in view of Applicants argument that the

cited prior art does not teach GPR3 comprising the amino acid sequence of SEQ ID NO: 46.

Claim Rejections under 35 USC § 101 and 112, 1st paragraph

(i). 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

(ii). Claims 1-3, 8, 10, and 20-25 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" context of use for the claimed invention which does not require further research.

Claims 1-3, 8, 10, and 20-25 are drawn to a method for directly identifying an agonist or inverse agonist of an endogenous, constitutively active G protein coupled orphan receptor using a GPCR fusion protein comprising an endogenous, constitutively active G protein coupled orphan receptor and a G protein, The utility analysis for the claimed methods is based upon the utility of the agonists and antagonists screened by the method. Since neither the prior art nor the specification discloses the biological functions of the orphan G protein coupled receptor GPR3 and a patentable utility of the agonists and antagonists, the claimed method does not have a patentable utility.

First, an orphan cell surface receptor, such as GPR3, has no known ligand and is not necessarily linked to any known biological functions, any known diseases or medical conditions, there is no specific and substantial utility for an orphan cell surface receptor and thus for a method of identifying an agonist or inverse agonist using the orphan receptor. It clearly requires further research for an artisan to confirm a "real world" context of use, that is, to determine the biological functions of the orphan cell surface receptor used in the screening method of the present invention. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966), noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."

Second, MPEP§2107.01 states that many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). MPEP further states that an assessment that focuses on whether an invention is useful only in a research setting thus does not address whether an invention is useful in a patent sense. Instead, Office personal must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention.

Furthermore, MPEP§2107.01 clearly lists that a method of assaying for or identifying a material that itself has no specific and/or substantial utility does not have a specific and substantial utility.

(iii). Claims 1-3, 8, 10, and 20-25 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

(iv). Response to Applicants' argument

Applicants argue that the subject invention should not be limited to a single orphan receptor, as it finds use in directly identifying a candidate compound a an agonist or inverse agonist of any endogenous, constitutively active G protein coupled orphan receptor, not just a single one. Applicants argue that restricting the utility analysis only to GPR3 is improper and request the full scope of claimed invention be considered by the Office in analyzing its utility. Applicants argue that examples of orphan GPCRs with known functional activity have been described in the art as well as in the application as filed.

Applicants' argument has been fully considered, but is not deemed to be persuasive because as indicated in the petition decision mailed on 08/25/2011, the elected GPR3 (SEQ ID NO: 46) will continue to be starting place for examination. In applications

containing a Markush-type claim that encompasses at least two independent or distinct inventions, the examiner may require a provisional election of a single species prior to examination on the merits. An examiner should set forth a requirement for election of a single disclosed species in a Markush-type claim using form paragraph 8.01 when claims limited to species are present or using form paragraph 8.02when no species claims are present. See MPEP § 808.01(a) and § 809.02(a). Following election, the Markush-type claim will be examined fully with respect to the elected species and further to the extent necessary to determine patentability. If the Markush-type claim is not allowable, the provisional election will be given effect and examination will be limited to the Markush-type claim and claims to the elected species, with claims drawn to species patentably distinct from the elected species held withdrawn from further consideration. See MPEP803.02.

At the first paragraph of page 6 of Applicants' response, Applicants argue that the disease-specific expression pattern of GPR3 does indeed provide the impetus for screening for candidate agonist/inverse agonist compounds of GPR3.

Applicants' argument has been fully considered, but is not deemed to be persuasive because a higher expression level in brain biopsy tissue from subjects suffering from epilepsy as compared with control tissue does not establish a causal link between the GPR3 and epilepsy and does not provide a patentable utility for the agonist of GPR3. Likewise, the impetus for screening for candidate agonist/inverse agonist compounds of

GPR3 does not provide a specific and substantial utility for an agonist/inverse agonist of the GPR3 to be screened because an orphan cell surface receptor, such as GPR3, has no known ligands and is not necessarily linked to any known biological functions, any known diseases or medical conditions, it clearly requires further research for an artisan to confirm a “real world” context of use, that is, to determine the biological functions of the orphan cell surface receptor and thus the agonists/inverse agonists.

Beginning at the 2nd paragraph of page 6 of Applicants' response, Applicants argue the following:

> In response, Applicants again maintain that the utility of the claimed invention is derived not from the specific identity of the orphan GPCR employed in the method, but rather from the ability of one to use the claimed methods to identify modulating compounds for virtually any orphan GPCR that is of interest to them. Thus, similar to the way that the utility of PCR is not tied to one specific polynucleotide sequence of interest (i.e., a sequence to be amplified), the utility of the subject invention is not tied to a specific orphan GPCR to be screened.
>
> As established above and in prior responses, Applicants submit that there existed, at the time the application was filed, orphan GPCRs with known functional properties and that identifying modulatory compounds for such functionally-characterized orphan GPCRs represents a specific, substantial “real world” use of the claimed invention. The fact of the existence of orphan GPCRs having no known function does no more to negatively impact the real world utility of the claimed invention than does the existence of nucleic acid sequences having no known function negatively impact the real world utility of PCR.

Applicants' argument has been fully considered, but is not deemed to be persuasive because MPEP§2107.01 clearly lists that a method of assaying for or identifying a material that itself has no specific and/or substantial utility does not have a specific and substantial utility.

Claim Rejections under 35 U.S.C. 103 (a)

(i). The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

(ii). Claims 1-3, 10, 20, 21, 23, and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Li et al. (U.S. Patent No. 5,998,164, Dec. 7, 1999; 102 (e) date: June 6, 1995) in view of Eggerick et al. (Biochem. J. 309:837-843, 1995) and Seifert et al (J. Biol. Chem. 273: 5109-5116, February 27, 1998).

Li et al. teach a method of screening for an agonist of an orphan G protein-coupled receptor GPR3, comprising providing cells expressing the receptor, contacting the expressed receptor with a test compound to observe stimulation or inhibition of a functional response, and determining whether the test compound activates the receptor (column 11, the 4th paragraph to the 8th paragraph). The cells expressing the receptor include cells from mammals (column 11, line 39). Li et al. further teach formulation of a pharmaceutical composition comprising an agonist of GPR3 (column 13, the 7th paragraph; column 1, 2nd paragraph).

Li et al. do not teach (i). a GPCR fusion protein comprising an endogenous,

constitutively active orphan G protein coupled receptor and a G protein used in the instantly claimed method; and (ii). screening for an inverse agonist (with respect to claim 2).

Eggerick et al. teach a GPR3 polypeptide comprising an amino acid sequence that is 99.9% identical to the amino acid sequence of SEQ ID NO: 46 of the present invention, i.e., the GPR3 polypeptide of Eggerick et al. differs from the GPR3 polypeptide of SEQ ID NO: 46 of the present invention only at position 320 (see attached sequence alignment). Eggerick et al. teach that the GPR3 is an endogenous, constitutively active orphan G protein coupled receptor. Eggerick et al. teach that the GPR3 is Gs-activating orphan receptor and constitutively activates adenylate cyclase (see, e.g., Abstract).

Seifert et al. teach a method of determining effects of an agonist or an inverse agonist of β2AR on GTPase and adenylyl cyclase activity in cells expressing a fusion protein comprising β2AR and Gsα (β2AR Gsα; see Abstract; Figures 2 and 3). Seifert et al. teach that fusion of β2AR to Gsα promotes efficient coupling (Abstract).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the method of Li et al. to identify an agonist or inverse agonist of orphan GPR3 using a GPCR fusion protein comprising GPR3 of Eggerick et al. and a Gs protein with a reasonable expectation of success. One would have been motivated to do so because such a fusion protein promotes efficient coupling as taught

by Seifert et al. (see e.g., Abstract).

(iii). Response to Applicants' argument

Applicants argue that the GPR3 taught by Li et al. is not the same GPR3 taught in the subject application. Applicants' argument has been fully considered, but is not deemed to be persuasive because claims 1-3, 10, 20, 21, 23, and 24 are not limited to GPR3 of SEQ ID NO: 46.

Beginning at the last paragraph of page 8 of Applicants' response, Applicants argue the following:

> As is clear from the above section, Li et al. is merely providing a general description of screening assays for agonists or antagonists of GPCRs, and not for agonists or inverse agonists of orphan GPCRs as claimed. Indeed, as reproduced above, Li et al. describes identifying an antagonist of a receptor (e.g., a GPCR) by contacting a cell expressing the receptor ***with a known ligand*** and a compound to be screened. Inhibition of ligand activation indicates that the compound is an antagonist of the receptor. Thus, in order to screen for antagonists, this section of Li et al. describes using ***a known ligand*** for the receptor. As such, this section is not drawn to screening orphan receptors, in which the ligand is by definition not known.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, in addition to the above teachings, Li et al. also teach a method of screening for an agonist of an orphan G protein-coupled receptor GPR3, comprising providing cells expressing the receptor, contacting the expressed receptor with a test compound to observe stimulation or inhibition of a functional response, and determining whether the test compound activates the receptor (column 11, the 4th

paragraph to the 6th paragraph). Secondly, Li et al. teach a number of orphan G protein coupled receptors, including GPR3 (column 1, the 2nd paragraph). Moreover, one of skill in the art would know that the general screen methods would be applicable to g protein coupled receptors, including orphan G protein coupled receptors.

Beginning at the 4th paragraph of page 9 of Applicants' response, Applicants argue that Seifert et al. teach the generation and testing of different β2-adrenoreceptor/Gsα fusion proteins. Applicants argue that β2-adrenoreceptor is not an orphan G protein coupled receptor.

Applicants' argument has been fully considered, but is not deemed to be persuasive because this is a 103(a) rejection which is based upon the combined teaching of the cited art. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The publication of Seifert et al. is cited here to show that fusion of β2AR to Gsα promotes efficient coupling, which would motivate one of skill in the art to modify the method of Li et al. to identify an agonist or inverse agonist of orphan GPR3 using a GPCR fusion protein comprising GPR3 of Eggerick et al. and a Gs protein.

At the 3rd paragraph of page 10 of Applicants' response, Applicants argue the following:

> Eggerick is cited by the Office merely for its teaching that GPR3 is a constitutively activated orphan GPCR. As such, Eggerick et al. fails to remedy the above-identified deficiencies in the teachings of Li et al. and Siefert, namely (i) a GPCR fusion protein comprising an endogenous, constitutively active orphan G protein coupled receptor and a G protein used in the instantly claimed method; (ii) screening for an agonist or an inverse agonist of the constitutively active GPCR; and (iii) the claimed identifying step.

Applicants also argue that the GPR3 of Li et al. is not the same as the GPR3 of Eggerick et al. and that the relevance of the teaching of Li et al. is unclear.

Applicants' argument has been fully considered, but is not deemed to be persuasive because this is a 103(a) rejection which is based upon the combined teaching of the cited prior art. As noted above, claims 1-3, 10, 20, 21, 23, and 24 are not limited to GPR3 of SEQ ID NO: 46. Eggerick et al. teach that GPR3 is an endogenous, constitutively active orphan G protein coupled receptor. The GPR3 polypeptide of Eggerick et al. differs from the GPR3 polypeptide of SEQ ID NO: 46 of the present invention only at position 320. On the other hand, the reference of Li et al. is cited for screen methods. The cited prior art together teaches or suggests the instantly claimed invention.

Claim Rejections under Obviousness-Type Double Patenting

(i). The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11

F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

(ii). Claims 1-3, 10, and 20 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 6,653,086. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Claims 1-3, 10, and 20 of the instant application are drawn to a method for directly identifying an agonist or inverse agonist of an endogenous, constitutively active G protein coupled orphan receptor using a GPCR fusion protein comprising an endogenous, constitutively active G protein coupled orphan receptor and a G protein, whereas claims 1-3 of U.S. Patent No. 6,653,086 is drawn to the same method except that a GPCR fusion protein comprising an endogenous, constitutively active G protein coupled orphan receptor and a Gsα protein. Therefore, the patented claims are related to the instant claims as species to genus with respect to G protein. A patented species (an endogenous, constitutively active G protein coupled orphan receptor and a Gsα

protein) renders its genus (a GPCR fusion protein comprising an endogenous, constitutively active G protein coupled orphan receptor and a G protein) obvious and thus anticipates the genus.

Conclusion

No claims are allowed.

Advisory Information

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875.

The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

/Ruixiang Li/
Primary Examiner, Art Unit 1646
September 13, 2011

/GEORGE C ELLIOTT/
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